## REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

***Status of the Claims***

In the present Amendment, claim 5 has been canceled without prejudice or disclaimer of the subject matter contained therein. Also, claims 1 and 6 have been amended. Thus, claims 1-4 and 6 are pending in the present application.

No new matter has been added with the present amendments. In fact, the amendments to claims 1 and 6 are clarifying in nature and are not narrowing in scope. By amending these terms in order to clarify the claimed invention (e.g., "characterized by" to "said method comprising"), Applicants are in no way conceding any limitations with respect to the interpretation of the claims under the Doctrine of Equivalents.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

***Issues under 35 U.S.C. § 102(b) and § 103(a)***

Claim 5 stands rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative under 35 U.S.C. § 103(a) as being unpatentable over **Shimizu *et al.*** (*Blood,* Vol. 10, pp. 3688-3692 (1996)) (see pages 2-4 of the Office Action).

Also, claims 1-4 and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Zanjani *et al.*** (*International J. Hematol.,* Vol. 63, pp. 179-192 (2001)) in view of **Li *et al.*** (*Blood,* Vol. 98, pp. 335-342 (1996)), **Sone *et al.*** (*Circulation,* Vol. 107, pp. 2085-2088 (2003)) and **Hamaguchi *et al.*** (*Blood,* Vol. 93, pp. 1549-1556 (1999)) (see pages 4-6 of the Office Action).

Applicants respectfully traverse all rejections, and reconsideration is based on the following remarks.

Claim 5

Claim 5 has been canceled, thereby rendering these rejections moot. Withdrawal of both rejections in view of Shimizu *et al.* is respectfully requested.

Claims 1-4 and 6

Applicants respectfully submit the one of ordinary skill in the art would not combine the disclosures of Zanjani *et al.*, Li *et al.*, Sone *et al.* and Hamaguchi *et al.* in order to achieve the presently claimed invention.

First, Applicants note M.P.E.P. § 2143 which sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in

*Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Here, the Examiner has not appropriately resolved the *Graham* factors, including ascertaining the differences between the prior art and the claims that are at issue, and the rationales in combining the cited references are improper.

In the Office Action, the Examiner states that the present invention is obvious, wherein:

- the cited primary reference of Zanjani *et al.* discloses the preparation of human/sheep hematopoietic chimeras by engraftment of human hematopoietic cells in fetal sheep;
- the cited secondary reference of Li *et al.* refers to the effectiveness of BMP-4 for hematopoietic differentiation of ES cells;
- the cited secondary reference of Sone *et al.* refers to the effectiveness of OP9 cells for hematopoietic differentiation; and
- the cited secondary reference of Hamaguchi *et al.* refers to the effectiveness of co-culturing with OP9 cells for hematopoietic differentiation.

However, in the present invention, an embryonic stem cell is transplanted to fetal sheep so as to prepare human/sheep hematopoietic chimeras. The Examiner's assertion that the present invention in using embryonic stem cells is obvious over the cited combination of references using hematopoietic stem cells is not reasonable, and such rationales are improper. There have been many attempts to do what the Examiner is asserting, yet it is understood in the art that it is not a matter of combining various ingredients together and differentiation simply occurs.

Applicants herein attach scientific literature to support Applicants' position, which is an article by M. Kyba and G.Q. Daley (*Experimental Hematology*, Vol. 31 (11), pp. 994-1006 (2003)). The *Experimental Hematology* (2003) article descibes the difficulty in preparing adult hematopoietic chimeras from embryonic stem cells (differentiation of hematopoietic stem cells). Specifically, in the section titled "Hematopoietic from ES cells: primitive or definitive?", the paragraph spanning the left and right columns on page 996, Kyba *et al.* disclose:

> Since the first demonstration of blood differentiation in EBs, many groups have attempted to transplant EB-derived cells into conditioned adult recipients. Although the failure of EB-derived cells to generate spleen colonies (CFU-S) has been documented [24], the many failed attempts to generate
>
> adult hematopoietic chimeras for the most part have not been published. In the two decades that have passed since the initial observation of blood differentiation from ES cells, there have been a few sporadic reports of success. One study

Thus, the *Experimental Hematology* (2003) article describes that many attempts to generate adult hematopoietic chimeras have failed (e.g., "In the two decades that have passed . . . there have been a few sporadic reports of success."). Further, many of the failed attempts are not

even published. As noted above, the present invention is the first to achieve a preparation of monkey/sheep hematopoietic chimeras using adult sheep from ES cells of primates, which was considered to be very difficult to achieve at the time the present application was filed. Accordingly, the present invention is not rendered obvious by the cited combination of references.

Though the Examiner refers to rationales A, B, E and F from the *KSR Int'l* decision, *supra*, in the Office Action (see paragraph bridging pages 5-6), the cited rationales are not applicable here. It also appears rationale G has been applied (see Office Action, page 5, second paragraph), which is also improper. For instance, rationales A, B and F refer to "predictable results" or the variations being predictable. However, the record in this application clearly establishes that the results are not predictable. As explained above, as there are many problems in the art. Regarding rationales E and G, Applicants respectfully traverse application of these rationales as one of ordinary skill in the art understands that there is no reasonable expectation of success and/or motivation also as explained above (e.g., many attempts to generate adult hematopoietic chimeras have failed).

Further, Applicants note that while the courts have adopted a more flexible approach in connection with the obviousness standard based on the *KSR v. Teleflex* case which involved a mechanical device in a relatively predictable technological area, it remains true that, despite this altered standard, the courts recognize inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical

compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound, in a particular manner, in order to establish *prima facie* obviousness of a new compound) (no identification of a predictable solution where the prior art discloses a broad selection of compounds). Here, the state of the art (e.g., see the attached *Exp. Hematol.* (2003) article) shows that there have been many failed attempts in achieving the presently claimed invention, wherein failed attempts are typically not published. This is also another reason as to why the cited rationale E ("obvious to try") is improper.

In addition, the cited secondary references of Li *et al.*, Sone *et al.*, and Hamaguchi *et al.* merely describe that each factor (e.g., BMP-4) is effective for hematopoietic differentiation from embryonic stem cells. There is no guidance in these cited references for one of ordinary skill in the art to overcome the obstacles in achieving differentiation from an embryonic stem cell of a primate into a hematopoietic cell as instantly claimed. If anything, the references have been improperly cited and combined based on hindsight reconstruction. Furthermore, even if the disclosures were (hypothetically) combined, the present invention is still patentably distinct for the reasons mentioned above.

Finally, Applicants respectfully submit that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966); *see also* M.P.E.P. § 2143. Again, as mentioned, the results are not predictable to one of ordinary skill in the art.

Based on the above, Applicants respectfully submit that the present invention is patentably distinct from the cited combination of Zanjani *et al.*, Li *et al.*, Sone *et al.*, and Hamaguchi *et al.* Reconsideration and withdrawal of this rejection are respectfully requested.

*Conclusion*

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

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Respectfully submitted,

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Attachment:
M. Kyba and G.Q. Daley, *Experimental Hematology*, Vol. 31 (11), pp. 994-1006 (2003)